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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,235	12/19/2005	Alex Cimpoia	SHIRE-518	5723
23599 7590 01/23/2009 MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201				
EXAMINER				
ARIANI, KADE				
ART UNIT		PAPER NUMBER		
1651				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/535,235

Applicant(s)

CIMPOIA ET AL.

Examiner

KADE ARIANI

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 October 2008.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-24 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SF/ICE)
Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

The amendment filed on October 06, 2008, has been received and entered.

Claims 1-24 are pending in this application and were examined on their merits.

Claim Objection

The objection of Claims 1 and 12 is withdrawn due to Applicants amendments to the claims filed on 10/06/2008.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cimpoia et al. (WO 00/47759) in view of Janes et al. (in IDS, J. Org. Chem., 1999, Vol. 64, p.9019-9029) and Ferrero et al. (Monatshefte für Chemie, 2000, Vol. 131, p.585-616), and further in view of Adler et al. (JBC, 1961, Vol. 236, No.12, p.3240-3245).

Claims 1-11 are drawn to a process comprising the steps of a) subjecting a compound of formula II to an enzymatic resolution in the presence of pig liver esterase or porcine pancreatic lipase, b) recovering compound of formula I, wherein R_1 is C_{1-12} alkyl, and R_2 is $CO-C_{6-12}$ aryl, wherein R_1 is methyl and R_2 is benzoyl, the process further comprising a) replacing the functional group at position C4 of the compound of formula I to produce a compound of formula V, b) removing the R_2 group, c) recovering a compound of formula VI, wherein B is purine (or pyrimidine) base, wherein R_3, R_4, R_5, R_6, R_7 , and R_8 are H, and further recovering a compound of formula VII.

Claims 12-24 are drawn to a process for producing a compound of formula III comprising the steps of a) subjecting a compound of formula IV to an enzymatic resolution in the presence of lipase, b) recovering compound of formula III, wherein R_{11} is C_{1-12} alkyl and R_{12} is a hydroxyl protecting group $CO-C_{6-12}$ aryl, wherein R_{11} is methyl and R_{12} is benzoyl, wherein the enzyme is *Candida Antarctica* lipase A, *C. Antarctica* lipase B, *C. Lypolitica* lipase, *R. Miehei* lipase, the process further comprising a) replacing the functional group at position C4 of the compound of formula III to produce a compound of formula VIII, b) removing the R_{12} group, c) recovering a compound of formula IX, wherein B is purine (or pyrimidine) base, wherein R_3, R_4, R_5, R_6, R_7 , and R_8 are H, and further recovering a compound of formula X.

Cimpoia et al. teach a process of making dioxalane nucleoside analogs with a high degree of steric purity which includes the use of certain hydrolytic enzymes (p.7 2nd paragraph). Cimpoia et al. teach a process comprising the steps of a) subjecting a dioxolane compound (formula II, formula IV) to an enzymatic resolution in the presence

of horse liver esterase and various lipases, b) recovering the resulted compound, wherein R_1 is C_{1-12} alkyl, and R_2 is $CO-C_{6-12}$ aryl, wherein R_1 is methyl and R_2 is benzoyl (wherein R_{11} is C_{1-12} alkyl and R_{12} is a hydroxyl protecting group $CO-C_{6-12}$ aryl, wherein R_{11} is methyl and R_{12} is benzoyl), the process further comprising a) replacing the functional group at position C4 of the compound, removing the R_2 group (R_{12} group), recovering a compound of (formula VI, formula IX) wherein B is purine (or pyrimidine) base, wherein R_3, R_4, R_5, R_6, R_7 , and R_8 are H, and further recovering the compound of (formula VII, formula X) (see Abstract, page 4, page 7 2nd-4th paragraphs, page 8 2nd paragraph, page 11 2nd and 3rd paragraphs). Cimpoia et al. further teach modifications and variations of the present invention including but not limited to selection of enzymes and optimization of reaction conditions will be obvious (page 68 last paragraph).

Cimpoia et al. do not teach the enzyme is pig liver esterase, and *Candida Antarctica* lipase B. However, Ferrero et al. teach enzyme-catalyzed reactions have become standard procedures for the synthesis of enantiomerically pure compounds for their simple feasibility and high efficiency, the enzymes commonly used including pig liver esterase, porcine pancreas lipase, and *Antarctica* lipase B (p.586 Table.1. first column lines 2, 5 and 6).

Moreover, Janes et al. teach dioxolane nucleosides are powerful antiviral and anticancer drugs. Janes et al. further teach the commercial availability, relatively low cost, and tolerance for a wide class of substrates make hydrolytic enzymes attractive biocatalysts (Abstract, and p.9020 2nd column 2nd paragraph). Janes et al. teach using lipases to resolve key intermediates for synthesis of nucleoside analogues (p.9020 2nd

column 3rd paragraph). Janes et al. also teach commercially available lipases including *Antarctica* lipase A, and *C. Lyopolitica* lipase, *R. Miehei* lipase (p.9022, Table 1.) Janes et al. teach methods to rapidly screening a library of commercial hydrolases for activity and diastereoselectivity toward specific diastereomers (p.9021 1st column 2nd paragraph).

Further motivation to use pig liver esterase in the process of Cimpoia et al. is in Adler et al. who teach pig liver esterase has the same type of catalytic site as does horse liver esterase, and they display quite similar kinetic properties (p.3244 2nd column 3rd paragraph).

Therefore, in view of the above teachings, a person of ordinary skill in the art at the time the invention was made could have been motivated to modify the process as taught by Cimpoia et al. by substituting horse liver esterase with the pig liver esterase as taught by Ferrero et al. to provide a process for producing a compound with formula I (a dioxolane nucleoside analogue) with predictable results of hydrolyzing the substrate compound of formula II and recovering compound of formula I. The claimed method would have been obvious because substitution of horse liver esterase with pig liver esterase in the process of Cimpoia et al. would have yielded predictable results (enzymatic diastereomeric resolution) to one of ordinary skill in the art at the time the invention was made. The motivation as taught by Adler et al. would be because pig liver esterase and horse liver esterase displayed quite similar catalytic and kinetic properties. Moreover, a person of ordinary skill in the art at the time the invention was made could have been motivated to modify the process as taught by Cimpoia et al. by substituting

the lipase in the process of Cimpoia et al. with commercially available *Antarctica* lipase A (or *Antarctica* lipase C, *Lypolita* lipase, and *R. Miehei* lipase) as taught by Janes et al. with a reasonable expectation of success of selecting a lipase capable of hydrolyzing the substrate compound of formula IV. The motivation as taught by Janes et al. and Cimpoia et al. would be to select suitable enzymes and to optimize the reaction conditions.

Applicant is directed to pages 12-13 of *KSR v Teleflex* (500 US ____ 2007) " ...the Court has held that a "patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U. S. 147, 152 (1950). This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."

Response to Arguments

Applicant's arguments filed 10/06/2008 have been fully considered but they are not persuasive.

Applicant argues that Cimpoia et al. do not disclose the use of pig liver esterase.

However, as mentioned immediately above, at the time the invention was made a person of ordinary skill in the art would have recognized the interchangeability of pig

liver esterase and horse liver esterase. Thus, a person of ordinary skill in the art at the time the invention was made could have been motivated to substitute horse liver esterase in the process Cimpoa et al. with pig liver esterase with predictable results.

Applicant argues that the disclosure of Janes et al. actually teaches away from applicant's claimed invention, because, Janes et al. teach the tested enzymes exhibit insufficient estimated diastereoselectivity.

However, Janes et al. teach a method to rapidly screen a library of commercial hydrolases for activity and diastereoselectivity toward specific diastereomers. Janes et al. teach to identify selective enzymes (hydrolases), traditionally a researcher carries out several small-scale kinetic resolutions with commercially available hydrolases. Janes et al. teach in general a researcher does not test all available hydrolases so potentially selective hydrolases are likely missed. To increase our chance of finding a highly selective commercial hydrolase for activity and diastereoselectivity (p.9021 1st column 2nd paragraph). Thus, a person of ordinary skill in the art at the time the invention was made upon reading the teachings of Janes et al. could have been motivated to use the commercially available *Candida Antarctica* lipase A or B in the method as taught by Cimpoa et al. according to the teachings of Janes et al. to identify their activity and diastereoselectivity towards the claimed compounds.

Moreover, just because the tested enzymes showed insufficient diastereoselectivity towards specific diastereomers, would not discourage a person of ordinary skill in the art to test their selectivity towards other diastereomers.

Applicant argues that Cimpola et al. taken alone or in combination with Janes et al., and Ferrero et al. fails to render obvious Applicant's claimed invention.

As mentioned immediately above, Applicant is directed to pages 12-13 of KSR v Teleflex (500 US ____ 2007) " ... the Court has held that a "patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp., 340 U. S. 147, 152 (1950). This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kade Ariani whose telephone number is (571) 272-6083. The examiner can normally be reached on 9:00 am to 5:30 pm EST Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kade Ariani
Examiner
Art Unit 1651

/Leon B Lankford/
Primary Examiner, Art Unit 1651